UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,313	03/07/2005	Michael Bardroff	F2842 US S3 (C018016/0180	1924

7590 01/28/2008

Stephen M Haracz
Bryan Cave
1290 Avenue of the Americas
New York, NY 10104-3300

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,313	BARDROFF ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007 and 25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-16,22 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-16,22 and 28-30* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9,11-16,22 and 28-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/04, 8/6/07, 11/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' elections with traverse of Group I, claims 1-16, 22 and 28-30, and of species B) MSR-7 antibody, in the reply filed on 27 July 2007 are acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction and election of species requirements, the elections have been treated as elections without traverse (MPEP § 818.03(a)).

Response to Amendment

Claims 10, 17-21, 23-27 and 31-40 have been canceled as requested in the amendment filed on 25 October 2007. Following the amendment, claims 1-9, 11-16, 22, and 28-30 are pending in the instant application.

Claims 1-9, 11-16, 22, and 28-30 are under examination in the instant office action.

Sequence Rules Requirement

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Therefore, the application must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Therefore, the application must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). However the

instant application is not in compliance with the sequence rules, particularly 37 C.F.R. § 1.821(d), which requires that reference be made to a particular sequence identifier (SEQ ID NO:) in the specification and claims at each disclosure of a sequence encompassed by the definitions set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The instant claim 3 and supporting sections of the specification contain sequences, which are not properly identified.

In case these sequences are new, Applicants must provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification wherever a reference is made to that sequence. For rules interpretation Applicants may call (703) 308-1123. See M.P.E.P. 2420-2435. Applicants are advised to review the entire text of the instant specification for compliance with sequence rules.

Information Disclosure Statements

Signed and initialed copies of the IDS papers filed on 20 August 2004, 06 August 2007 and 13 November 2007 are enclosed in this action.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies or fragments thereof that comprise 6 CDRs, three from the VH domain and three from the VL domain, wherein the antibodies and fragments thereof bind the same antigen as claimed, does not reasonably provide enablement for an antibody and fragments thereof that do not contain a full set of 6 CDRs from the VH and the VL domains as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative

skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claims 4-6 are broadly drawn to antibodies or fragments thereof, comprising only a VH and/or a VL domain that do not contain a full set of 6 CDRs from the VH and the VL domains.

The specification discloses only antibodies that contain both a VH and a VL chain with no less than 6 CDRs, 3 from the VH chain and 3 from the VL chain that bind to antigen (see Table 1, pp.64-68). The specification does not enable antibodies and fragments thereof, which do not contain 6 CDRs and bind antigen.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first

column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). The Rudikoff et al. reference teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibodies and fragments thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing an antibody and fragments thereof containing fewer than 6 CDRs, resulting in an antibody that retains the antigen specificity currently claimed. However, the claim language also reads on small amino acid sequences, which are incomplete regions of the variable region of the antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly as is claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above, undue experimentation would indeed be required to make and use the invention commensurate with the scope of the claims.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

The invention appears to employ novel biological materials, specifically the MSR-3; MSR-7 and MSR-8 antibodies. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. It appears that Applicants have not deposited the biological materials, and a deposit at a recognized depository may be made for enablement purposes. If a deposit has been made under the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicants' attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information; however, Applicants are cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicants are advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims depend from canceled claims, i.e. claims 17 and 18 and 27, respectfully. Thus, the metes and bounds of claims 22 and 28 cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 9, 15, 16, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,955,317 to Suzuki et al (citation A3 on the IDS dated 13 November 2007.

The claims are directed to an antibody molecule capable of specifically recognizing two regions of the β-A4 peptide/A β4, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof

and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof.

The Suzuki et al. patent teaches a monoclonal antibody that specifically recognizes two regions of the β-amyloid (i.e., β-A4) peptide, wherein the two regions are the amino acid sequences of SEQ ID NO: 7 and SEQ ID NO: 10 (see claim 1, for example). The Suzuki et al. patent's SEQ ID NO: 7 is the amino acid sequence DAEFRHDSGYEVHHQKLVFFAEDVGSNK, which comprises both the instant SEQ ID NO: 1 and the instant SEQ ID NO: 2 (see cols. 47-48), and the Suzuki et al. patent's SEQ ID NO: 10 is the amino acid sequence DAEFRHDSGYEVHHQK, which comprises the instant SEQ ID NO: 1 and fragment of the instant SEQ ID NO: 2 (see cols. 49-50). Thus, the limitations of claims 1 are taught by the Suzuki et al. patent. Given that the antibody of the Suzuki et al. patent specifically recognizes the two regions claimed, the antibody would recognize at least two consecutive amino acids within the two regions, thus meeting the limitations of claim 2. Also, absent evidence to the contrary, the antibody would bind to at least one of the regions of SEQ ID NO: 1 and to at least one of the regions of SEQ ID NO: 2 recited by claim 3, thus meeting the limitations of claim 3. The patent teaches that the antibodies of the invention can be full-length, a F(ab)-fragment and a $F(ab)_2$-fragment (col.18, lines 10 and 11), thus meeting the limitations of claim 8. Moreover, given that the two regions of the β-A4 peptide are separated by at least 1 amino acid, the regions form a discontinuous or conformational epitope, thus meeting the limitations of claim 9. The patent also teaches pharmaceutical compositions (abstract), thus meeting the limitations of claims 15, 16, 29 and 30. It is

noted that claim 29 is a product-by-process claim. Given that the patent teaches the product itself, said claim is anticipated. A product made by any other process renders a product-by-process claim unpatentable. See In re Marosi, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985).

Since the patent teaches all the elements of the claims, claims 1-3, 8, 9, 15, 16, 29 and 30 are anticipated by U.S. Patent No. 5,955,317 to Suzuki et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,955,317 to Suzuki et al (citation A3 on the IDS dated 13 November 2007) in view of Knappik et al. (citation C3 on the IDS dated 20 August 2004).

The claims are drawn to a nucleic acid, vector and host cell that encode the antibody molecule capable of specifically recognizing two regions of the β-A4 peptide/A β4, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof.

The Suzuki et al. patent teaches as set forth above, but does not teach encoding nucleic acids, vectors or host cells. However, determining the amino acid sequence of the antibody and then the encoding nucleic acid is standard and known in the art as evidenced by the Knappik et al. reference (p.58, col.1). The Knappik et al. reference

teaches nucleic acid-vector-host cell expression and production of antibodies (p.58), as in the instant claims 11-14.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the antibody of the Suzuki et al. patent with the disclosure of the Knappik et al. reference. The skilled artisan would have been motivated to make these modifications to express the antibody recombinantly because of the advantages of doing so, as taught by the Knappik et al. reference (entire document, e.g., p.58, col.1). The person of ordinary skill in the art would have had a reasonable expectation of success because both references teach that the products and methods would work (entire documents).

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregory S. Emch/

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
22 January 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

Docket No.: F2842 US S3 (C018016/0180304)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Michael BARDROFF *et al.*	)	Examiner: G. S. Emch
Serial No.: 10/505,313	)	Art Unit: 1649
Filed: August 20, 2004	)	
For: **ANTI-AMYLOID BETA ANTIBODIES AND THEIR USE**	)	

New York, New York
June 30, 2008

RESPONSE TO OFFICE ACTION, INCLUDING AMENDMENT AND REQUEST FOR EXTENSION OF TIME

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Non-Final Office Action mailed January 28, 2008, which set a three-month shortened statutory period for response. A two-month extension of time to respond to the Office Action is hereby requested. Accordingly, this response is filed timely upon mailing, with an executed certificate of mailing, on or before June 30, 2008, as June 28th falls on a Saturday. 37 CFR §§ 1.7, 1.8 and 1.136. Enclosed is a check in the amount of $460.00 to cover the fee for the extension of time. 37 CFR § 1.17. Please charge any required extension-of-time fees, or any other fees, not otherwise paid by check to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

Please amend the application as follows:

AMENDMENTS TO THE SPECIFICATION begins on page 3 of this paper.

AMENDMENTS TO THE CLAIMS are reflected in the listing of claims, which begins on page 10 of this paper.

REMARKS begin on page 16 of this paper.

IN THE SPECIFICATION

Please delete paragraph 17 and replace with the following:

[0017] The term "two regions of the β-A4 peptide" relates to two regions as defined by their amino acid sequences shown in SEQ ID NOs: 1 and 2, relating to the N-terminal amino acids 2 to 10 and to the central amino acids 12 to 25 of β-A4 peptide. The term " β-A4 peptide" in context of this invention relates to the herein above described Aβ39, Aβ41, Aβ43, preferably to Aβ40 and Aβ42. Aβ42 is also depicted in appended SEQ ID NO: 27. It is of note that the term "two regions of the β-A4 peptide" also relates to an "epitope" and/or an "antigenic determinant" which comprises the herein defined two regions of the β-A4 peptide or parts thereof. In accordance with this invention, said two regions of the β-A4 peptide are separated (on the level of the amino acid sequence) in the primary structure of the β-A4 peptide by at least one amino acid, preferably by at least two amino acids, more preferably by at least three amino acids, more preferably by at least four amino acids, more preferably by at least five amino acids, more preferably at least six amino acids, more preferably at least nine amino acids and most preferably at least twelve amino acids. As shown herein and as documented in the appended examples, the inventive antibodies/antibody molecules detect/interact with and/or bind to two regions of the β-A4 peptide as defined herein, whereby said two regions are separated (on the primary structure level of the amino acid sequence) by at least one amino acid

and wherein the sequence separating said two regions/"epitope" may comprise more then ten amino acids, preferably 14 amino acids, more preferably 15 amino acids or 16 amino acids. For example, MSR-3 Fab (as an inventive antibody molecule) recognizes detects/interacts with two regions on the β-A4 peptide, wherein said first region comprises amino acids 3 and 4 (EF) and said second regions comprises amino acids 18 to 23 (VFFAED, SEQ ID NO: 421). Accordingly, the separating sequence between the region/epitopes to be detected/recognized has a length of 13 amino acids on the primary amino acid sequence structure. Similarly, MSR #3.4H7 IgG1, an optimized and matured antibody molecules derived from MSR-3 and comprised in an IgG1-framework, detects/interacts with/binds to two epitopes/regions of β-A4 which comprise in the first region positions 1 to 4 (DAEF) and in the second region positions 19 to 24 (FFAEDV, SEQ ID NO: 423) of β-A4 as defined herein. Accordingly, MSR #3.4H7 IgG1 recognizes/detects/interacts with/binds to two epitopes/regions which are, on the primary amino acid sequence level, separated by 14 amino acids. As detailed in the appended examples, affinity maturation and conversion of monovalent inventive Fab fragments to full-length IgG1 antibodies may result in a certain broadening of the epitopes/regions detected in pepspot, ELISA assays and the like. Therefore, the antibody molecules of the invention are capable of simultaneously and independently recognizing two regions of the β-A4 peptide/Aβ4 wherein said regions comprise the amino acid sequence as

shown in SEQ ID NO: 1 (or parts thereof) and the amino acid sequence as shown in SEQ ID NO: 2 (or (a) part(s) thereof). Due to the potential broadening of epitopes as detailed herein it is, however, also envisaged that amino acids in close proximity to the sequences of SEQ ID NO: 1 and 2 are detected/recognized, i.e. that additional amino acids are part of the two regions to be detected/recognized. Accordingly, it is also envisaged that, e.g. the first amino acid of Aβ (1-42) as defined herein, namely D (Aspartic acid) in part of one epitope to be detected/recognized or that amino acids located after the region of Aβ (1-42) as defined in SEQ ID NO: 2 are detected/recognized. Said additional amino acid may, e.g., be the amino acid on position 26 of SEQ ID NO: 27 (βA4/Aβ (1-42)), namely S (Serine).

Please deleted the last three sentences of paragraph 18 and replace with the following three sentences:

-- Preferred fragments or parts are in the first region/stretch of SEQ ID NO: 27 the amino acid sequences AEFRHD (SEQ ID NO: 415), EF, EFR, FR, EFRHDSG (SEQ ID NO: 416), EFRHD (SEQ ID NO: 417) or HDSG (SEQ ID NO: 418), and in the second region/stretch of SEQ ID NO: 27 the amino acid sequences HHQKL (SEQ ID NO: 419), LV, LVFFAE (SEQ ID NO: 420), VFFAED (SEQ ID NO: 421), VFFA (SEQ ID NO: 422) or FFAEDV (SEQ ID NO: 423). As mentioned above, said fragments may also comprise additional amino acids or may be parts of

the fragments defined herein. Specific examples are DAE, DAEF, FRH or RHDSG. --

Please delete paragraph 37 and replace with the following paragraph:

--[0037] In a preferred embodiment, the antibody molecule of the invention recognizes at least two consecutive amino acids within the two regions of Aβ4 defined herein, more preferably said antibody molecule recognizes in the first region an amino acid sequence comprising the amino acids: AEFRHD (SEQ ID NO: 415), EF, EFR, FR, EFRHDSG (SEQ ID NO: 416), EFRHD (SEQ ID NO: 417) or HDSG (SEQ ID NO: 418), and in the second region an amino acid sequence comprising the amino acids: HHQKL (SEQ ID NO: 419), LV, LVFFAE (SEQ ID NO: 420), VFFAED (SEQ ID NO: 421), VFFA (SEQ ID NO: 422) or FFAEDV (SEQ ID NO: 423). Further fragments or broadened parts comprise: DAE, DAEF, FRH or RHDSG.--

Please add the following sentence to the end of paragraph 169:

-- The V_H DNA sequence of the IgG of antibody molecule 7.9H7 after subcloning is shown in SEQ ID No.: 424, and the corresponding amino acid sequence is shown in SEQ ID No: 425.

Please delete paragraph 206 and replace with the following paragraph:

-- [0206] Employing specific of the above described heptapeptides derived from Aβ, specific ELISA-tests as described herein above were carried out. Preferably, inventive antibodies comprise antibodies which show, as measured by of optical densities, a signal to background ratio above "10" when their reactivity with an A-beta derived peptide (AEFRHD, SEQ ID NO: 415; amino acid 2 to 7 of A-beta) is compared to an non-related protein/peptide like BSA. Most preferably, the ratio of optical densities is above "5" for a corresponding reaction with at least one of the following three Aβ derived peptides: (VFFAED, SEQ ID NO: 421; amino acid 18 to 23 of Aβ) or (FFAEDV, SEQ ID NO: 423; amino acid 19 to 24 of Aβ) or (LVFFAE, SEQ ID NO: 420; amino acid 17 to 22 of Aβ). --

Please delete the first row of Table 6 and replace with the following language:

--Reactivity of MS-R Fabs with BSA-conjugated Abeta heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. --

Please delete paragraph 208 and replace with the following paragraph:

-- [0208] Table 6: Reactivity of MS-R Fabs with BSA-conjugated Abeta heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. --

Please delete paragraph 209 and replace with the following paragraph:

-- [0209] Table 7: Reactivity of MS-R IgGs and mouse monoclonal antibodies BAP-1, BAP-2, 4G8, 6E10 Amy-33 and 6F/3D with BSA-conjugated Aβ heptapeptides 2-7 (AEFRHD, SEQ ID NO: 415), 17-22 (LVFFAE, SEQ ID NO: 420), 18-23 (VFFAED, SEQ ID NO: 421) and 19-24 (FFAEDV, SEQ ID NO: 423). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. *this antibody is specific for sequence 8-17 and does not recognize N-terminal or middle epitope sequences. --

In Column 2, Row 1 of Table 7, please insert "(SEQ ID NO: 415)" after "AEFRHD." In Column 3, Row 1 of Table 7, please insert "(SEQ ID NO: 420)" after "LVFFAE." In Column 4, Row 1 of Table 7, please insert "(SEQ ID NO: 421)" after "VFFAED". In Column 5, Row 1 of Table 7, please insert "(SEQ ID NO: 423)" after "FFAEDV".

Please cancel the Sequence Listing as filed in the original application.

Please enter the Substitute Sequence Listing set forth in Exhibit 1 on the next page after the Abstract.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

LISTING OF CLAIMS:

Claim 1. (Currently Amended) An antibody molecule capable of specifically recognizing two regions of the β-A4 peptide/Aβ4, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof, wherein said antibody molecule comprises

(a) a variable V_L-Region comprising complementary determining regions, L-CDR1, L-CDR2, L-CDR3, wherein:

(1) L-CDR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 96, 130-133, 141-143, 160, 175-177, 180, 189, 190, 200, 201, 206-211, and 224;

(2) L-CDR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 97, 144, 161, and 212; and

(3) L-CDR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 16, 18, 20, 75, 77, 79, 81, 83, 85, 87, 95, 98, 102, 103-107, 145, 149-159; 162, 166, 178, 183, 202, 213, 217, 218, 220, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411 and 413; and

(b) a variable V_H-Region comprising complementary determining regions, H-CDR1, H-CDR2, H-CDR3, wherein:

(1) H-CDR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 99, 146, 163, 203, and 214;

(2) H-CDR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 100, 108-129, 134-140, 147, 164, 167-174, 179, 181, 182, 184-188, 191-199, 204, 205, 215, 219, and 221-223; and

(3) H-CDR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 22, 24, 26, 61, 63, 65, 67, 69, 71, 73, 93, 101, 148, 165, 216, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, and 383.

Claim 2. (Original) The antibody molecule of claim 1, wherein said antibody molecule recognizes at least two consecutive amino acids within the two regions of β-A4.

Claim 3. (Currently Amended) The antibody molecule of claim 1, wherein said antibody molecule recognizes in the first region an amino acid sequence ~~comprising:~~ selected from the group consisting of ~~AEFRHD~~, EF, EFR, FR, ~~EFRHDSG, EFRHD or HDSG~~ and SEQ ID NOs: 415 – 418, and in the second region an amino acid sequence ~~comprising:~~ selected from the group consisting of ~~HHQKL~~, LV, ~~LVFFAE, VFFAED, VFFA or FFAEDV~~ and SEQ ID NOs: 419 - 423.

Claim 4. (Previously presented) The antibody molecule of claim 1, wherein said antibody molecule comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of

SEQ ID NOs: 3, 5 and 7, or a variable V_H-region as shown in a SEQ ID NO: selected from the group consisting of SEQ ID NOs: 4, 6 and 8.

Claim 5. (Previously presented) The antibody molecule of claim 1, wherein said antibody molecule comprises a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 9, 11 and 13, or a variable V_L-region as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 10, 12 and 14.

Claim 6. (Currently Amended) The antibody molecule of claim 1, wherein said antibody molecule comprises at least one CDR3 amino acid sequence of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 17 or 19, or at least one CDR3 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 16, 18 or 20; and/or wherein said antibody molecule comprises at least one CDR3 amino acid sequence of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25, or at least one CDR3 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 22, 24 or 26.

Claim 7. (Previously presented) The antibody molecule of claim 1, wherein said antibody is selected from the group consisting of MSR-3, -7 and -8, and an affinity-matured version of MSR-3, -7 and -8.

Claim 8. (Previously presented) The antibody molecule of claim 1, wherein said antibody molecule is a full antibody (immunoglobulin), a F(ab)-fragment, a $F(ab)_2$-fragment, a single-chain antibody, a chimeric antibody, a CDR-grafted antibody, a bivalent antibody-construct, a synthetic antibody or a cross-cloned antibody.

Claim 9. (Previously presented) The antibody molecule of claim 1, wherein said two regions of β-A4 form a conformational epitope or a discontinuous epitope.

Claim 10. (Cancelled).

Claim 11. (Previously presented) A nucleic acid molecule encoding an antibody molecule according to claim 1.

Claim 12. (Original) A vector comprising the nucleic acid molecule of claim 11.

Claim 13. (Original) A host cell comprising the vector of claim 12.

Claim 14. (Previously presented) A method for the preparation of an antibody molecule comprising culturing the host cell of claim 13 under conditions that allow synthesis of said antibody molecule and recovering said antibody molecule from said culture.

Claim 15. (Previously presented) A pharmaceutical or diagnostic composition comprising an antibody molecule according to claim 1 and a carrier or diluent.

Claim 16. (Previously presented) The composition of claim 15, which is a pharmaceutical composition.

Claims 17-21. (Cancelled).

Claim 22. (Currently Amended) A kit comprising an antibody molecule according to claim 1, a nucleic acid molecule according to claim **[[16]]** 11, a vector according to claim **[[17]]** 12 or a host cell according to claim **[[18]]** 13, wherein the

antibody, nucleic acid, vector or host cell is contained in at least one vial, bottle, container or multicontainer unit.

Claims 23-28. (Cancelled).

Claim 29. (Previously presented) A composition comprising an antibody molecule produced by the method of claim 14.

Claim 30. (Previously presented) The composition of claim 16 further comprising a pharmaceutically acceptable carrier and/or diluent.

Claims 31-40. (Cancelled).

Claim 41. (New) An antibody molecule comprising

(a) a variable V_L-Region comprising complementary determining regions, L-CDR1, L-CDR2, L-CDR3, wherein:

(1) L-CDR1 comprises SEQ ID NO: 143;

(2) L-CDR2 comprises SEQ ID NO: 144; and

(3) L-CDR3 comprises SEQ ID NO: 95; and

(b) a variable V_H-Region comprising complementary determining regions, H-CDR1, H-CDR2, H-CDR3, wherein:

(1) H-CDR1 comprises SEQ ID NO: 146;

(2) H-CDR2 comprises SEQ ID NOs: 192; and

(3) H-CDR3 comprises SEQ ID NOs: 93.

Claim 42. (New) The antibody molecule according to claim 41, wherein the antibody is of the IgG1 subtype.

Claim 43. (New) The antibody molecule according to claim 41, wherein the variable V_H-region comprises SEQ ID NO: 89; and the variable V_L-region region comprises SEQ ID NO: 91.

Claim 44. (New) The antibody molecule according to claim 43, wherein the antibody is of the IgG1 subtype.

Claim 45. (New) The antibody molecule according to claim 41, wherein the variable V_H-region comprises SEQ ID NO: 425; and the variable V_L-region region comprises SEQ ID NO: 91.

Claim 46. (New) The antibody molecule according to claim 45, wherein the antibody is of the IgG1 subtype.

Claim 47. (New) A pharmaceutical composition comprising an antibody molecule according to claim 41 and a pharmaceutically acceptable carrier or diluent.

Claim 48. (New) A pharmaceutical composition comprising an antibody molecule according to claim 44 and a pharmaceutically acceptable carrier or diluent.

Claim 49. (New) A pharmaceutical composition comprising an antibody molecule according to claim 46 and a pharmaceutically acceptable carrier or diluent.

REMARKS

Amendments to the Specification

The specification has been amended (at paragraphs 17, 18, 37, 206, 208, 209; and Tables 6 and 7) to insert parenthetical references to new SEQ ID NOs. 415-423, corresponding to sequences longer than four amino acids that were disclosed in the specification but were not previously included in the Sequence Listing. These sequences (also recited in the original claim 3) are also included in the accompanying Substitute Sequence Listing.

Support for the amendments noted above are found in original claim 3, and in the specification at, for example, paragraphs 17, 18, 37, 206, 208, and 209, as well as Tables 6 and 7. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

The specification is also amended at paragraph 169 (page 69, lines 12-18) to provide reference to new SEQ ID NOs: 424-425. Conforming additions have also been made to the accompanying Substitute Sequence Listing.

Supporting disclosure for new SEQ ID NOs 424-425 is found, e.g., in paragraph 169. As described in paragraph 169, after sub-cloning from Fab into IgG, the nucleic acid sequence of the V_H chains (including that of SEQ ID NO: 88, which encodes SEQ ID NO: 89) changed from "c/aattg" to "g/aattg," resulting in an amino acid change from Q to E. These changes in nucleic acid and amino acid sequence are reflected in SEQ ID NOs: 424-425. The difference between SEQ ID NO: 424 and SEQ ID NO: 88 is a single nucleotide: the seventh nucleotide of SEQ ID NO: 88 is "c," whereas the seventh nucleotide of SEQ ID NO: 88 is "g." Similarly, SEQ ID NO: 425

differs from SEQ ID NO: 89 in that the third amino acid of SEQ ID NO: 89, "Q," has been changed to "E."

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments are respectfully solicited.

Amendments to the Claims

Claim 1 has been amended to recite that the antibody molecules have specific V_L and V_H structures, based upon the various sequences comprising the six CDRs of the antibodies. Support for this amendment may be found in the specification at, for example, page 15, lines 3-15; page 16, lines 18-29; page 17, lines 3-8 and lines 25-31; page 18, lines 16-19; page 19, lines 1-5, lines 8-13, and lines 22-31; page 20, lines 1-18; Table 1 (pages 64-68); Example 13 (pages 87-95); and the Substitute Sequence Listing. The Examiner will note that the SEQ ID NOs recited in claim 1 correspond to the amino acid sequences listed in Table 1.

Claim 3 has been amended to recite "SEQ ID NOs: 415 – 418" and "SEQ ID NOs: 419 – 423," the nine SEQ ID NOs that correspond to peptide residues previously described by single letter amino acid designations. Support for this amendment may be found in the original claim 3, the specification (and as amended) at, for example, paragraphs 18 and 37, and the Substitute Sequence Listing. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Claim 6 has been amended to recite "...CDR3 amino acid sequence" in two instances to parallel the other recitations of "CDR3 amino acid sequence" in the same claim. Support for this amendment may be found in the original claim 6. (*Id.*)

Claim 22 has been amended to recite "[a] kit comprising an antibody molecule according to claim 1, a nucleic acid molecule according to claim 11, a vector according to claim 12 or a host cell according to claim 13..." Support for this amendment may be found in the specification at, for example, paragraph 88.

Claim 28 has been cancelled, without prejudice.

Claims 41-49 have been added. These claims are directed to particular antibodies defined respectively by the sequences comprising their six CDRs.

Support for claim 41 may be found in the specification at, for example, page 18, lines 4-11; page 67, line 6; and in the Sequence Listing (SEQ ID NOs: 93, 95, 143, 144, 146, and 192.) Support for claim 42 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claim 43 may be found in the specification at, for example, page 18, lines 4-11. Support for claim 44 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claim 45 may be found in the specification at, for example, paragraph 169 (page 69, lines 12-18 as filed; and as amended above on page 6 of this Response), and the Substitute Sequence Listing (SEQ ID NO: 91 and 425). Support for claim 46 may be found in the specification at, for example, page 17, lines 3-11; and page 18, lines 17-22. Support for claims 47-49 may be found in the specification at, for example, page 28, lines 14-15.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments are respectfully solicited.

Sequence Listing Objection

The Office Action indicated that the application as filed failed to comply with the sequence rules of 37 C.F.R. §§ 1.821 through 1.825, and in particular, 37 C.F.R. § 1.821(d), "which requires that reference be made to a particular sequence identifier (SEQ ID NO:) in the specification and claims at each disclosure of a sequence encompassed by the definitions set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2)." (Paper No. 20080117 at 3). The Examiner asserted that "claim 3 and the supporting sections of the specification contain sequences, which are not properly identified." (*Id.*) The Examiner further stated that "[i]n case these sequences are new, Applicants must provide a substitute computer readable form (CRF) copy of a 'Sequence Listing' which includes all of the sequences that are present in the instant application and encompassed by these rules..." (*Id.*)

These alleged errors have been remedied by the amendments to claim 3, amendments to the specification, as well as the Substitute Sequence Listing, as set forth above in the "Amendment to the Specifications" and the "Amendments to the Claims" sections.

Accordingly, the previous Sequence Listing has been cancelled and a Substitute Sequence Listing in both hard copy and computer readable format are submitted herewith as Exhibits 1 and 2, respectively. Pursuant to 37 CFR § 1.821(f), undersigned counsel hereby represents that, upon information and belief, the content of the paper and computer readable Substitute Sequence Listings enclosed herewith are the same and that no new matter has been added.

It is believed that the amended specification, the amended claim 3, as well as the Substitute Sequence Listing and computer readable form presented herewith place the captioned application into compliance with the requirements set forth in 37 CFR § 1.821 *et seq.* Entry of the Substitute Sequence and withdrawal of the objection with respect to the Sequence Listing is respectfully solicited.

Indefinteness Rejection

Claims 22 and 28 were rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No. 20080117 at 9). In making the rejection, the Examiner asserted that the claims "depend from canceled claims, i.e. claims 17 and 18 and 27, respectfully." (*Id.*).

Claim 22 has been amended to depend from pending claims. Claim 28 has been cancelled.

Thus, it is respectfully submitted that the indefiniteness rejection has been rendered moot and should be withdrawn.

Enablement Rejection

a. Claims 4-6

Claims 4-6 were rejected under 35 USC §112, first paragraph, on the asserted grounds that the specification "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims." (Paper No. 20080117 at 4).

In making the rejection, the Examiner asserted that the specification "does not reasonably provide enablement for an antibody and fragments thereof that do not contain a full set of 6 CDRs from the [V_H] and the [V_L] domains as broadly encompassed by the claims." (*Id.*) The Examiner, however, acknowledged that the specification is "enabling for antibodies or fragments thereof that comprise 6 CDRs, three from the [V_H] domain and three from the [V_L] domain, wherein the antibodies and fragments thereof bind the same antigen as claimed." (*Id.*)

As discussed above, independent claim 1 has been amended to recite the sequences of all 6 CDRs, three from the V_H domain and three from the V_L domain. Because claims 4-6 depend from claim 1, these dependent claims incorporate the limitations of claim 1. In view of the amendment and the Examiner's acknowledgment, it is respectfully submitted that the enablement rejection of claims 4-6 should be withdrawn.

b. Claim 7

Claim 7 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. (Paper No. 20080117 at 6). In making the rejection, the Examiner asserted that "[t]he invention appears to employ novel biological materials, specifically the MSR-3, MSR-7 and MSR-8 antibodies." (*Id.* at 7) The Examiner further asserted that "[s]ince the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public." (*Id.*) In addition, the Examiner asserted, "[t]he specification does not disclose a repeatable process to

obtain the biological materials and it is not apparent if the biological materials are readily available to the public." (*Id.*)

For reasons set forth below, the rejection is respectfully traversed.

The specification sets forth the amino acid sequences (and encoding nucleic acid sequences) of the variable regions of MSR-3, MSR-7, and MSR-8 antibodies. For example, page 14, lines 16-20 and lines 24-27 disclose the following:

> The sequences as shown in SEQ ID NOs: 3 and 4 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-3 (MS-Roche 3), the sequences in SEQ ID NOs: 5 and 6 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-7 (MS-Roche 7) and SEQ ID NOs: 7 and 8 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-8 (MS-Roche 8)... SEQ ID NOs: 9 and 10 correspond to the V_L-region of MSR-3, SEQ ID NOs: 11 and 12 correspond to the V_L-region of MSR-7 and SEQ ID NOs: 13 and 14 correspond to the V_L-region of MSR-8.

With the disclosure of both the amino acid and the encoding nucleic acid sequences, a person skilled in the art may readily construct the MSR-3, MSR-7, and MSR-8 antibody molecules. Furthermore, the six CDRs of affinity-matured versions of the antibodies are disclosed, for example, in Table 1. Thus, affinity-matured versions may also be readily reproduced. Accordingly, the specification disclose repeatable processes for obtaining the biological material as set forth in claim 7.

For the above reasons, it is respectfully submitted that the enablement rejection of claim 7 should be withdrawn.

Anticipation Rejection

Claims 1-3, 8, 9, 15, 16, 29 and 30 were rejected under 35 U.S.C. 102(b) as anticipated by Suzuki *et al.*, U.S. Patent No. 5,955,317 ("Suzuki"). (Paper No. 20080117 at 9).

In making the rejection, the Examiner asserted that Suzuki discloses "a monoclonal antibody that specifically recognizes two regions of the β-amyloid (i.e., β -A4) peptide, wherein the two regions are the amino acid sequences of SEQ ID NO: 7 and SEQ ID NO: 10." (Paper No. 20080117 at 10). The Examiner further asserted that "Suzuki['s] SEQ ID NO: 7 is the amino acid sequence DAEFRHDSGYEVHHQKLVFFAEDVGSNK, which comprises both the instant SEQ ID NO: 1 and the instant SEQ ID NO: 2..., and the Suzuki['s] SEQ ID NO: 10 is the amino acid sequence DAEFRHDSGYEVHHQK, which comprises the instant SEQ ID NO: 1 and [a] fragment of the instant SEQ ID NO: 2 (see cols. 49-50)." (*Id.*) The Examiner then contended that "[t]hus, the limitations of claims 1 are taught by the Suzuki." (*Id.*)

Reconsideration and withdrawal of the rejection is respectfully requested.

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984).

First, it is respectfully submitted that the Examiner has misinterpreted the Suzuki reference. In particular, Suzuki does not disclose any antibody which recognizes any two nonoverlapping regions of amyloid beta 1-42, much less the two specific nonoverlapping regions recited in claim 1. To the contrary, Suzuki distinguishes antibodies based on their respective abilities to bind/not bind to unspecified amino acids contained within overlapping peptide residues, such as amino acids 1-28 (the Suzuki SEQ ID NO: 7 mentioned by the Examiner) and amino acids 1-16 (the Suzuki SEQ ID NO: 10 mentioned by the Examiner). Thus, Suzuki does not identically describe the antibodies recited in claim 1.

Moreover, claim 1 has been amended to recite that the antibody comprises six CDRs having specific amino acid sequences. By contrast, Suzuki does not describe the antibody sequence of any CDR, much less the sequences of all six CDRs of any antibody. Thus, Suzuki cannot anticipate claims 1 as amended.

Because claims 2-3, 8, 9, 15, 16, 29, and 30 depend from claim 1, they incorporate the language of claim 1 and thus are distinguishable from Suzuki for the same reasons as discussed above.

Accordingly, it is respectfully submitted that the anticipation rejection has been rendered moot and should be withdrawn.

Obviousness Rejection

Claims 11-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki in view of Knappik *et al.*, "Fully synthetic Human Combinatorial Antibody Libraries (HuCAL) Based on Modular Consensus

Frameworks and CDRs Randomized with Trinucleotide," *J. Mol. Biol.* 296: 57-86 (2000) ("Knappik"). (Paper No. 20080117 at 12).

In making the rejection, the Examiner acknowledged that Suzuki "does not disclose encoding nucleic acids, vectors or host cells." (*Id.*) To fill the knowledge gap, the Examiner relied on Knappik and asserted that "determining the amino acid sequence of the antibody and then the encoding nucleic acid is standard and known in the art as evidenced by [] Knappik... (p.58, col.1)." (*Id.*)

The obviousness rejection is respectfully traversed.

Obviousness **must** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993).

The rejection of claims 11-14 rests upon an unsupported conclusion that some amino acid sequences not identified by the Examiner, and indeed not described in Suzuki, are "obvious". From that platform, the Examiner then concludes that the particular nucleic acid sequences recited in claims 11-14 are obvious. The rejection is thus not based on facts, as is required.

Further, claims 11-14 incorporate the functional and structural limitation recited in amended claim 1, and thus the nucleic acid molecule recited in these claims encodes or produces antibodies having six CDR regions comprising specific amino acid sequences. Suzuki's antibodies are different functionally and structurally, and their encoding nucleotides are different from and not suggestive of the nucleic acids of claims 11-14.

Knappik does not fill the factual gaps left by Suzuki. Hence, the proposed combination of Suzuki and Knappik do not disclose or suggest claims 11-14.

Accordingly, for the reasons set forth above, entry of the amendments and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on June 30, 2008.

Jihong Zang, Reg. No. 56,606

Respectfully submitted,

By: _____

Stephen M. Haracz
Registration No. 33,397
Jihong Zang
Registration No. 56,606
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
Phone: (212) 541-2000
Fax: (212) 541-4630